XXX Congresso Nazionale ANTE - DIALISI E TECNOLOGIA
"Presente e futuro della Nefrologia Italiana"

AKI-D in ICU e non ICU, la stessa patologia? Come la trattiamo?

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Sala Congressi Hotel Mediterraneo

Riccione

Acute Kidney Injury treated with Dialysis: Differences between ICU and non-ICU setting

- **Are they the same pathology?**
- Are they treated at the same way?
- Do they have the same outcomes?

Introduction

- Whereas causes and outcome of AKI-D in ICU are described extensively, few data exist about AKI-D patients treated outside ICU (general or specialist medical or surgical departments).

- AKI-D has experienced a dramatic increase over a 20-years period. The epidemiology of AKI appears to be rapidly changing and this represents the most important challenge for the Nephrologist in the next few years.

Fagugli RM, Patera F, Battistoni S, Mattozzi F, Tripepi G. Six-year single-center survey on AKI requiring renal replacement therapy: epidemiology and health care organization aspects. J Nephrol. 2015; 28(3):339±49

In-hospital AKI

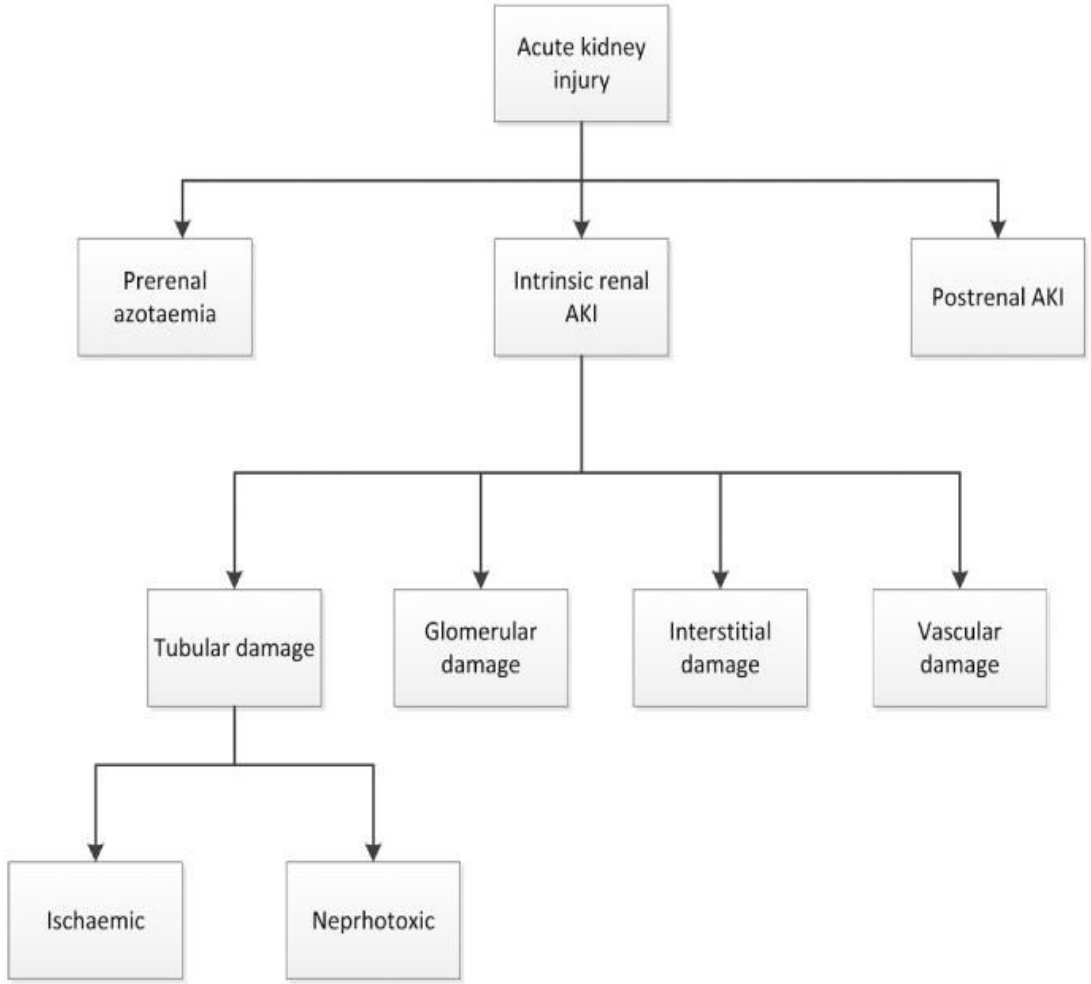
MORE THAN 50 % OF ICUs PATIENTS DEVELOP AKI

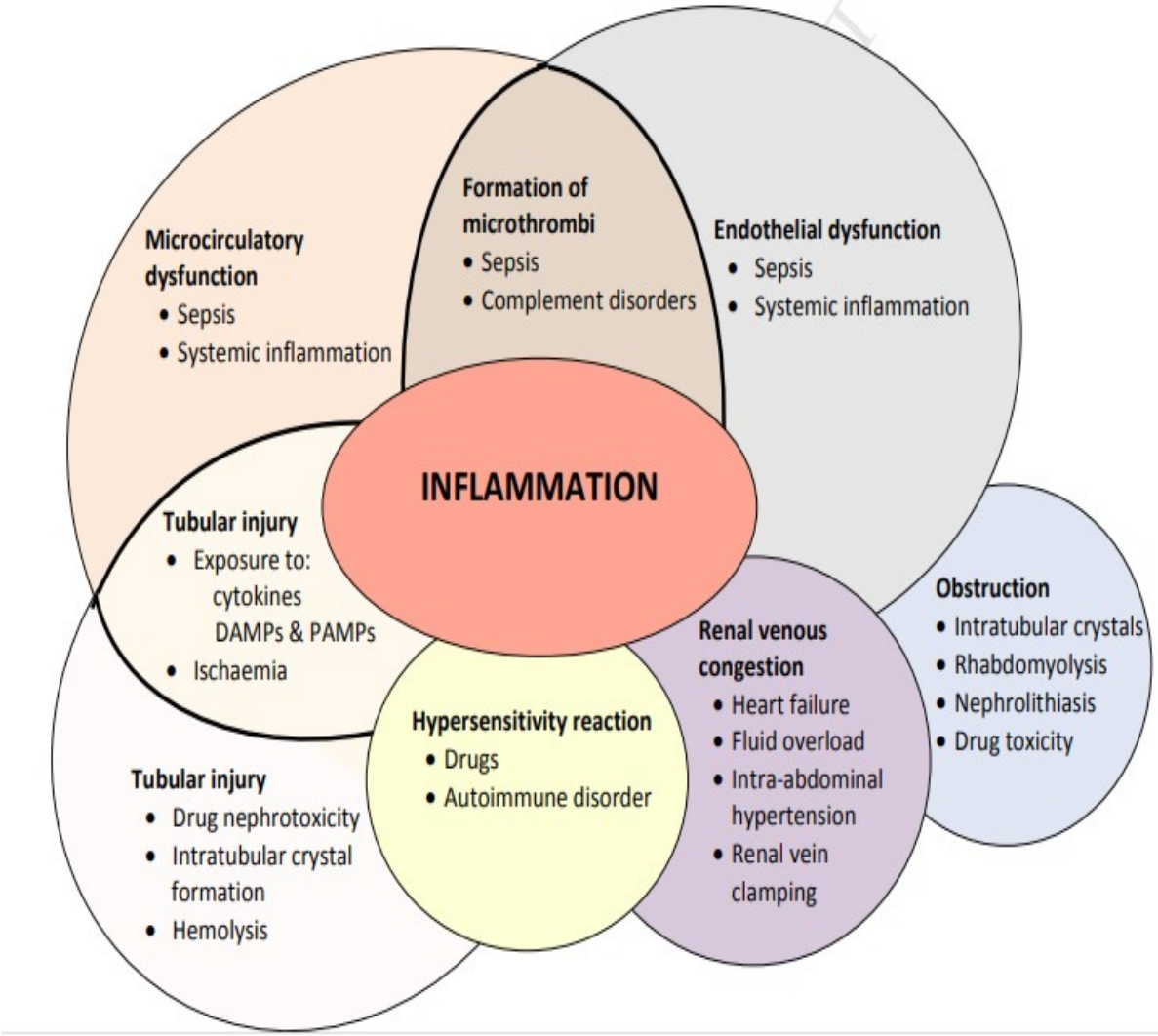
AKI INCREASES THE LENGHT OF HOSPITAL STAY

MORTALITY RATE IS INCREASED 5-TIMES IN ICU PATIENTS WITH AKI

ADDITIONAL ICU COSTS ARE ASSOCIATED WITH AKI

Etiology and pathophysiology of AKI





Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes

Ostermann M, Liu K, Pathophysiology of AKI, Best Practice & Research Clinical Anaesthesiology (2017)

AKI-D in the ICU: Epidemiology

- Sepsis associated AKI
- Surgery associated AKI
- AKI associated with hypoperfusion
- Nephrotoxic AKI

AKI in the ICU is Hospital-acquired in most cases

Kellum JA, Prowle JR (2018)
Paradigms of acute kidney injury in the **intensive care setting**.
Nat Rev Nephrol. 2018 Apr;14(4):217-230

MAIN SUPPOSED CAUSES OF AKI IN CRITICALLY ILL PATIENTS TREATED WITH CRRT (2022)

SEPSIS / SEPTIC SHOCK, 35%

COVID-19 INFECTION, 6%

CRUSH SYNDROME / POLITRAUMA, 8%

HEART DECOMPENSATION, 10%

HEPATO-RENAL SYNDROME, 9%

CARDIAC-SURGERY COMPLICATIONS, 1

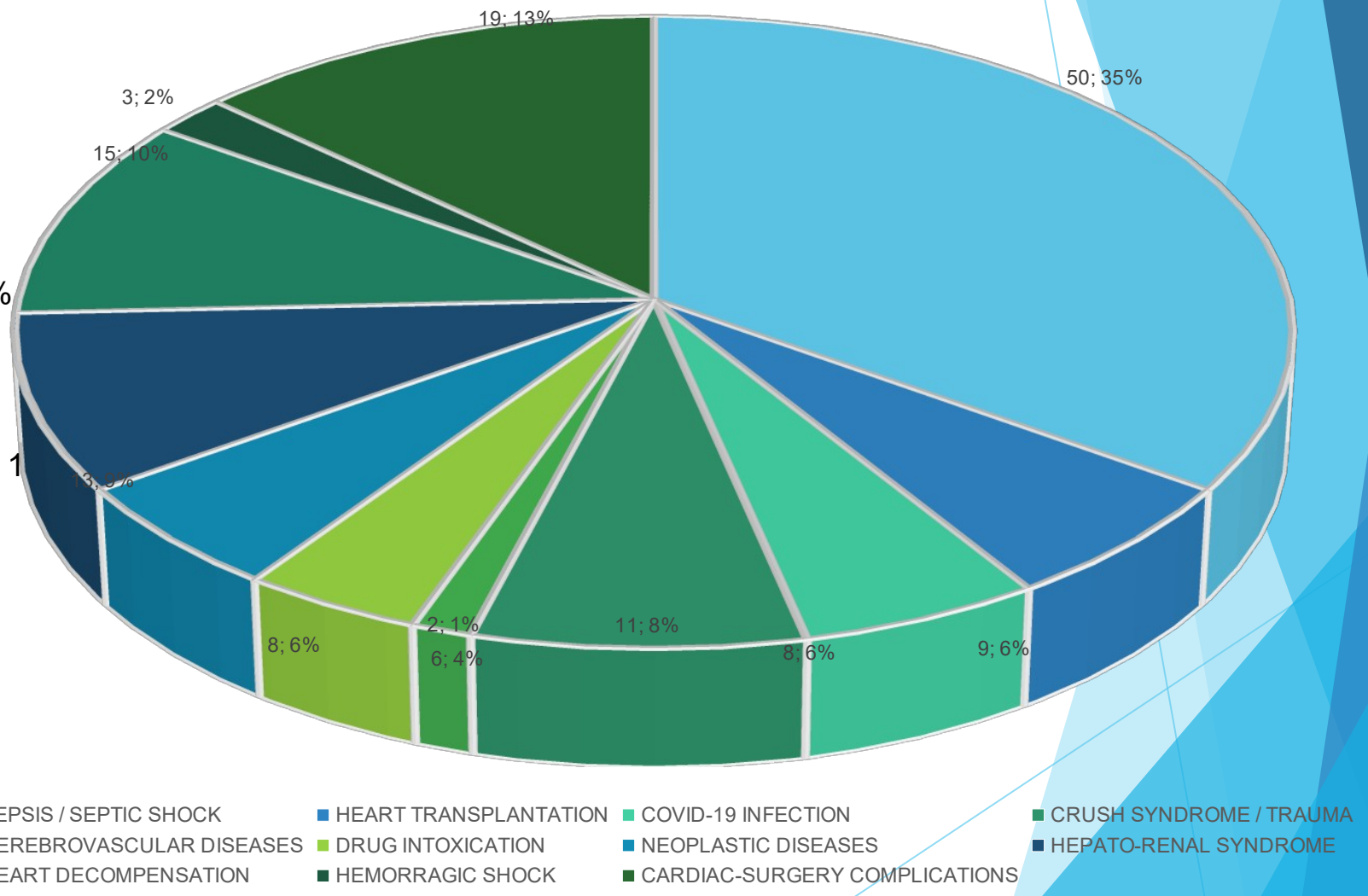
HEART TRANSPLANTATION, 6%

DRUG INTOXICATION, 4%

HEMORRAGIC SHOCK, 2%

CEREBROVASCULAR DISEASES, 1%

NEOPLASTIC DISEASES, 6%



AKI-D Outside the ICU: Epidemiology

Hemodynamic Group 68.7%

- Diarrhea 39.8%
- Septic diseases 17%
- Heart failure 13.6%
- Pneumonia 5.7%
- Acute coronary syndrome 4.6%

Non-Hemodynamic group 31.3%

- Interstitial nephritis 37.5%
- RPGN 10%
- Rhabdomyolysis 10%
- Cast nephropathy 7.5%
- Contrast induced AKI 7.5%
- Poisoning 5%

AKI-D outside ICU is community-acquired in 70.3% of cases

AKI-D treated outside the ICU is most often caused by renal hypoperfusion. It predominantly afflicts elderly patients with one or more comorbid conditions, who are treated with Diuretics and RASI and have an acute illness leading to volume depletion. Early discontinuation of these drugs may be a successful strategy to avoid AKI-D in vulnerable patients.

Sprenger-MaÈhr H, Zitt E, Lhotta K (2016)
Acute Kidney Injury Treated with Dialysis outside the Intensive Care Unit: A Retrospective Observational Single-Center Study. PLoS ONE 11

Table 3. Exposure to variant medication combination causing AKI-D.

	All	Hemodynamic	Non-hemodynamic	P*
	N (%)	N (%)	N (%)	
Diuretics and RASI	59 (46.1)	51 (58%)	8 (20.0%)	<0.001
Diuretics and RASI and NSAID	12 (9.4%)	10 (11.4%)	2 (5.0%)	0.34
Diuretics and NSAID	16 (12.5%)	12 (13.6%)	4 (10.0%)	0.78
RASI and NSAID	17 (13.3%)	13 (14.8%)	4 (10.0%)	0.58

Abbrevations: NSAID, non- steroidal anti-inflammatory drugs.

*group difference hemodynamic *vs* non-hemodynamic

doi:10.1371/journal.pone.0163512.t003

Table 4. Logistic regression analysis of risk factors for hemodynamic vs non-hemodynamic AKI-D.

Variable	Simple model		Multivariable model	
	OR (95% CI)	P	OR (95% CI)	P
Age (per year)	1.06 (1.03–1.10)	<0.001	1.05 (1.01–1.08)	0.015
Gender (1 = men, 0 = women)	0.45 (0.20–0.99)	0.048	0.44 (0.18–1.08)	0.073
RASI (1 = yes, 0 = no)	3.39 (1.56–7.39)	0.002	2.93 (1.23–6.98)	0.015
Loop diuretic (1 = yes, 0 = no)	4.71 (1.89–11.79)	0.001	3.48 (1.30–9.32)	0.013

Abbreviations: RASI, inhibitors of the renin-angiotensin-aldosterone system; OR, odds ratio; 95% CI, 95% confidence interval.

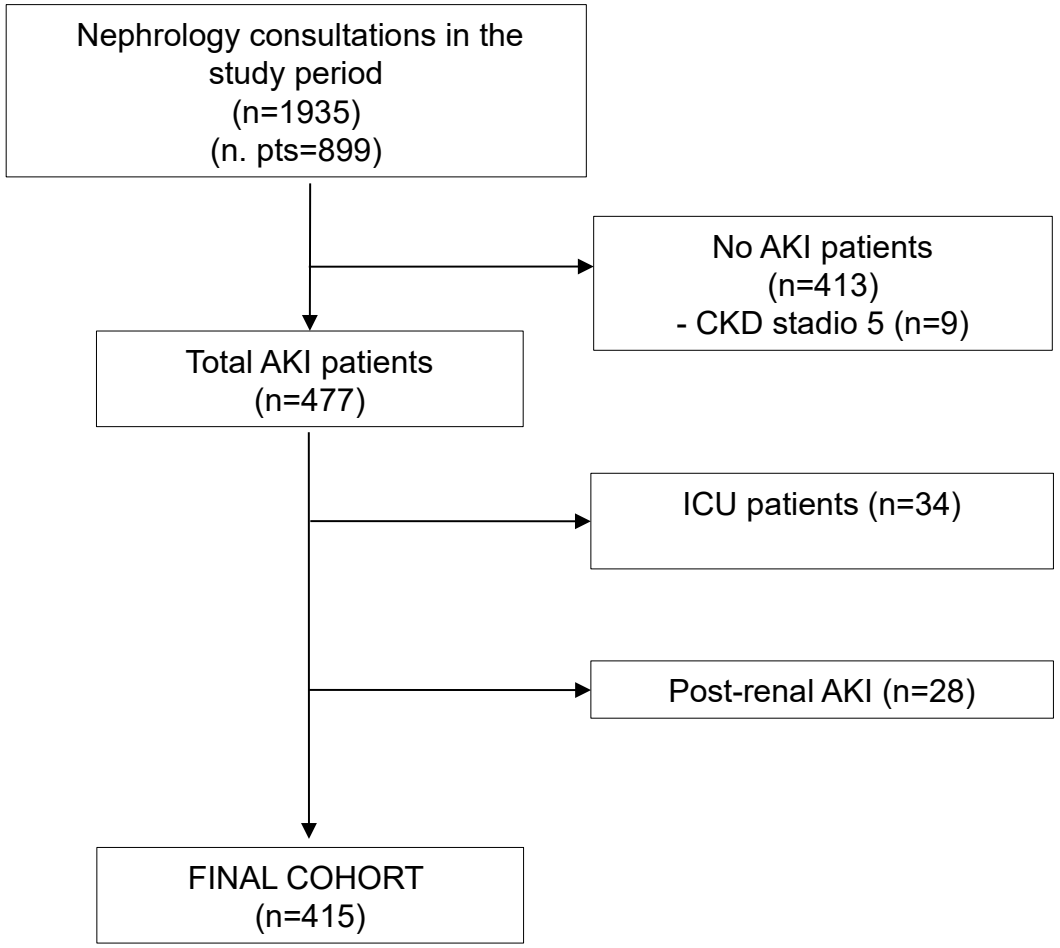
doi:10.1371/journal.pone.0163512.t004

Table 5. Renal and patient outcome.

	Non-hemodynamic	Hemodynamic	P
Recovery of kidney function	34 (85.0%)	69 (78.4%)	0.383
Death	5 (12.5%)	17 (19.3%)	0.343
Dialysis or death	7 (17.5%)	20 (22.7%)	0.502

doi:10.1371/journal.pone.0163512.t005

AKI in non critically ill patients

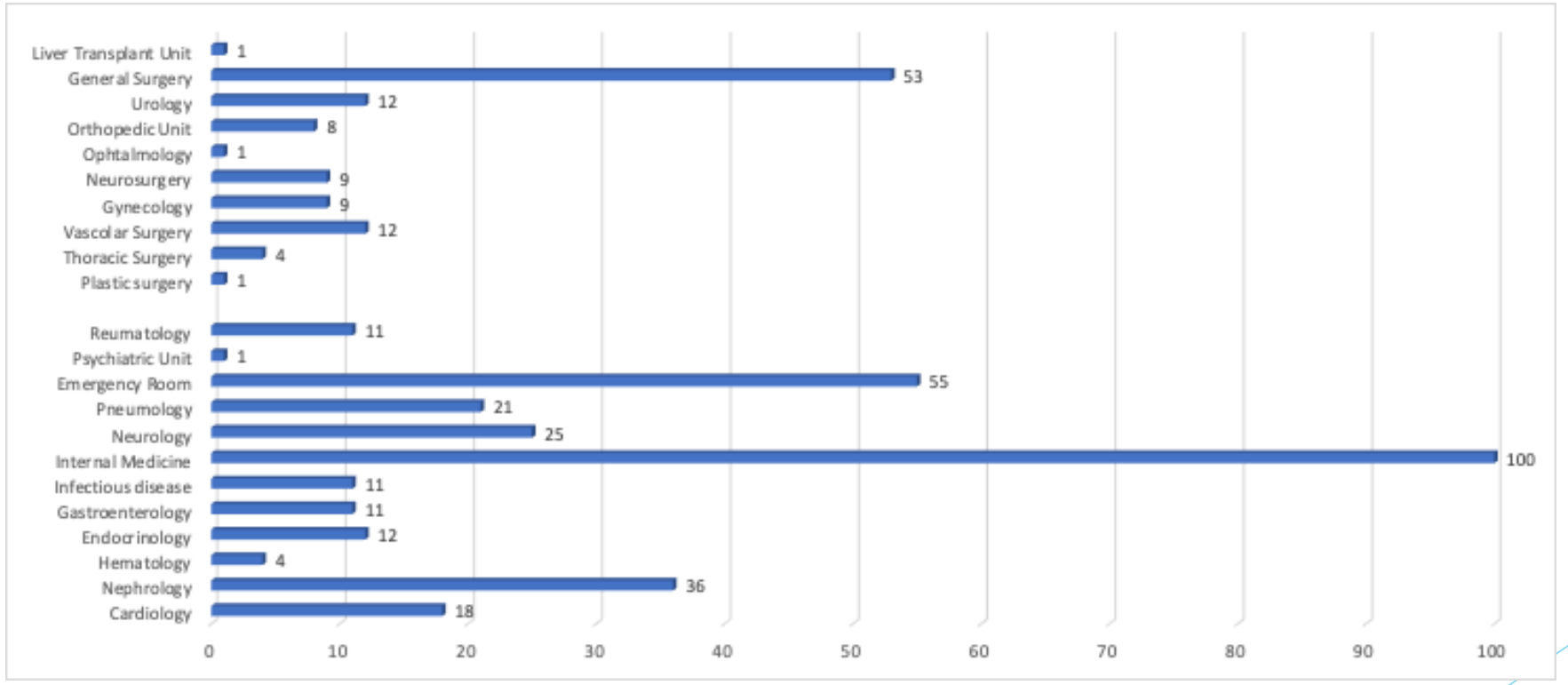


	All AKI patients (n=415)
Age, years, median (IQR)	76 (65-84)
Gender (M/F)	245 (59%) /170 (41%)
Baseline sCr, mg/dl, median (IQR)	1.3 (1–1.8)
Baseline estimated GFR, ml/min/1.73m^2, median (IQR)	52 (32-71)
Comorbidities	
Chronic kidney disease before hospital admission	
No CKD (eGFR >60 ml/min/1.73 m^2)	158
G3 (eGFR 30-59 ml/min/1.73 m^2)	137
G4 (eGFR 15-29 ml/min/1.73 m^2)	67
Unknown	53
Hypertension	184 (65.4%)
Cardiovascular disease	223 (53.9%)
Chronic respiratory disease	130 (31.3%)
Diabetes mellitus	127(30.6%)
Malignancy	112 (20.1%)
Hepatic disease	28 (6.8%)
Transplantation	16 (3.7%)
Length of hospital stay, days, median (IQR)	15 (8 - 26)
Time of nephrology consultation since hospital admission, days, median (IQR)	2 (0 - 6)

Fiorentino M et al, unpublished data

AKI settings

Medical wards	305 (73.5%)
Surgical wards	110 (26.5%)

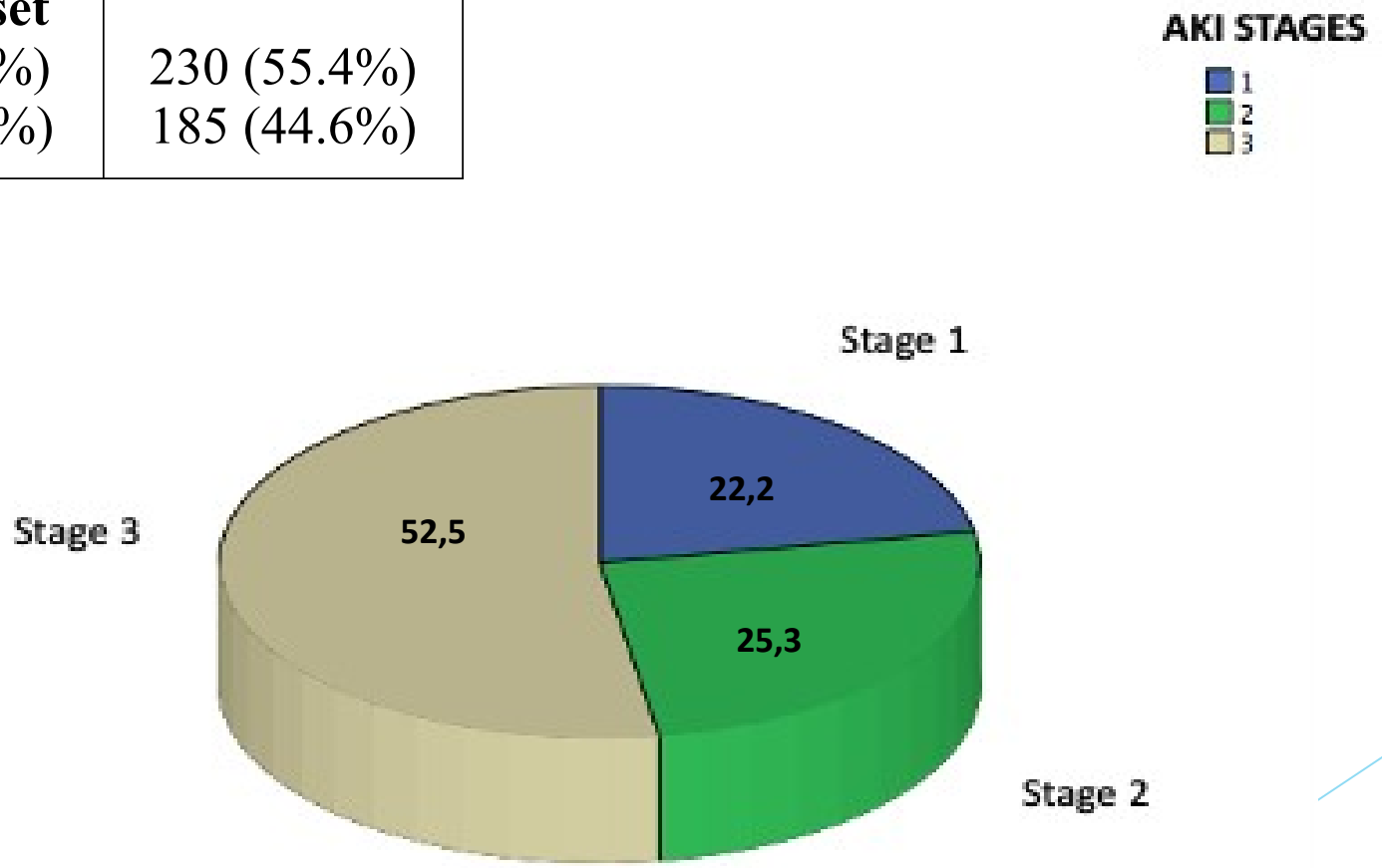


Number of patients

Fiorentino M et al, unpublished data

Timing of AKI episodes and staging

Timing of AKI onset	
•CA-AKI, n (%)	230 (55.4%)
•HA-AKI, n (%)	185 (44.6%)



Fiorentino M et al, unpublished data

Main supposed causes involved in AKI

	All patients (n=415)
Aetiology of AKI episodes Pre-renal, n (%) Renal, n (%)	 354 (85.3%) 61 (14.7%)
Renal hypoperfusion, n (%)	84 (20.4%)
Nephrotoxin exposures, n (%)	45 (10.9%)
Sepsis / septic shock, n (%)	168 (39.8%)
Major surgery, n (%)	14 (3.5%)
Cardiorenal Syndrome, n (%)	67 (16.3%)
Rapidly progressive glomerulonephritis, n (%)	22 (5.4%)
Hepatorenal Syndrome, n (%)	8 (2.1%)
Hemorrhagic shock, n (%)	7 (1.6%)

Fiorentino M et al, unpublished data

AKI episodes and main outcomes

	All patients (n=415)
Admission sCr, mg/dl	2.1 (1.3-3.5)
Admission eGFR, mg/dl	27 (15-47)
Peak sCr	3.3 (2.3-5)
Discharge sCr	1.7 (1.1-2.6)
Discharge eGFR	36 (19-63)
RRT-requiring AKI	54 (13%)
Days on AKI	16 (10-31)
Days on RRT	10 (3-20)
Renal recovery after AKI	197 (47.5%)
Dialysis dependence at hospital discharge	12 (2.9%)
Transfer to ICU	30 (7.2%)
Length of hospital stay, days, median (IQR)	15 (8 - 26)
In-hospital death	153 (36.9%)

Fiorentino M et al, unpublished data

Acute Kidney Injury treated with Dialysis: Differences between ICU and non-ICU setting

- Are they the same pathology?
- **Are they treated at the same way?**
- Do they have the same outcomes?

Renal replacement therapy in the ICU VS non-ICU setting

- The indications for commencement of RRT for AKI patients are the same for all modalities, such as fluid overload, hyperkalemia, acidosis and uremic syndrome that are refractory to medical therapy.

- The acute RRT available include:
- CRRT (continous renal replacement therapy);
- IHD (intermittent hemodialysis);
- Hybrid technique as SLED (sustained low efficiency dialysis) or SCUF (slow continous ultra-filtration)

Typical setting of different RRT modalities

	SCUF	CVVH	CVVHD	CVVHDF	PD	SLED	IHD
Blood flow (ml/min)	100–200	150–250	150–250	150–250	N/A	100–300	200–300
Predominant solute transport principle	convection	convection	diffusion	diffusion + convection	diffusion	diffusion	diffusion
Ultrafiltrate (ml/h)	100–300	1500–2000	variable	1000–1500	variable	variable	variable
Dialysate flow (ml/h)	0	0	1500–2000	1000–1500	1–2 l per exchange	100–300 ml/min	300–500 ml/min
Effluent volume (l/d)	2–8	36–48	36–48	36–72	24–48	N/A	N/A
Replacement fluid for zero balance (ml/h)	0	1500–2000	0	1000–1500	0	0	0
Urea clearance (ml/min)	1–5	25–33	25–33	25–33	variable	80–90	variable

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis, CVVHDF, continuous venovenous hemodialfiltration; IHD, intermittent hemodialysis; N/A, not applicable; PD, peritoneal dialysis; SCUF, slow continuous ultrafiltration; SLED, slow low-efficiency dialysis.

Renal replacement therapy in the ICU
VS non-ICU setting

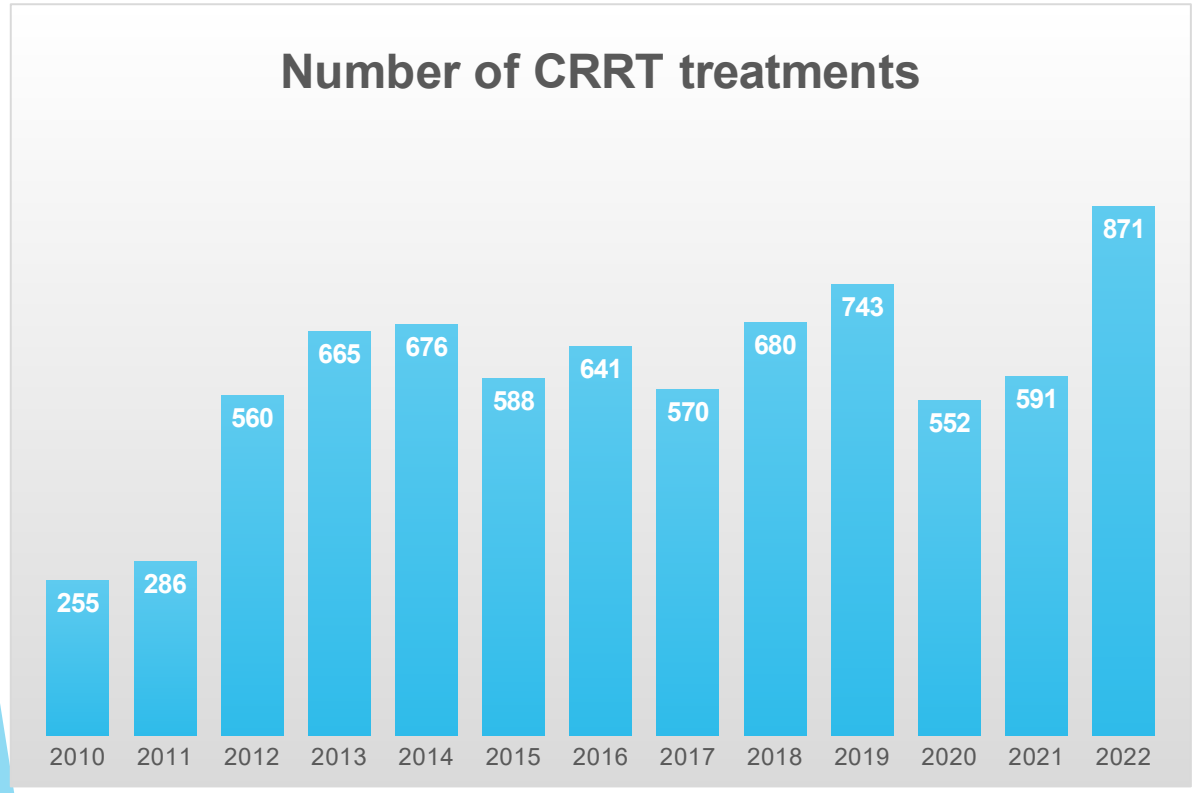
CRRT
(Continous renal replacement therapy)

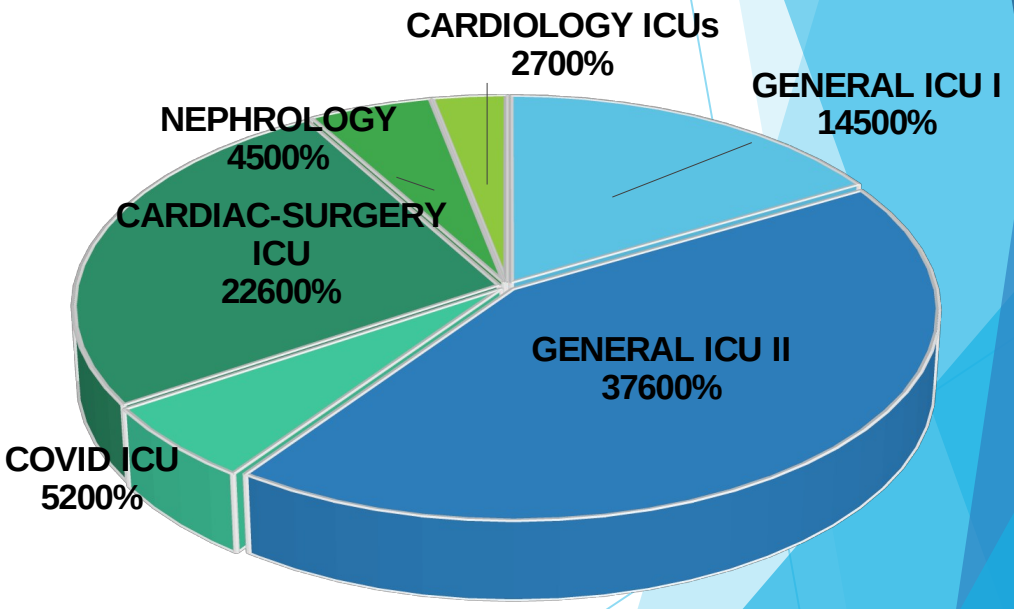
- Based on mechanism of solute transport, CRRT is divided into:
- CVVH (Continous veno-venous Haemofiltration) where solutes are removed by convection;
- CVVHD (Continous veno-venous HaemoDialysis) where solutes are removed by diffusion;
- CVVHDF (Continous veno-venous HaemoDiaFiltration) which combines convection and diffusion).

- **Advantages**
- Less cerebral edema;
- Prevention of fluid overload
- Optiimal kidney support for patients with hemodynamic instability

CRRT are the most used RRT in the contest of ICU setting.

CONTINOUS RENAL REPLACEMENT THERAPY (CRRT) IN CRITICALLY ILL PATIENTS ADMITTED IN INTENSIVE AND SUB-INTENSIVE CARE UNITs AT POLICLINICO - BARI





Renal replacement therapy in the ICU
VS non-ICU setting

IHD
(Intermittent Hemodialysis)

- IHD uses higher dialysate flow rates than CRRT

- **Advantages**
- Rapid removal of dialyzable substances
- Requires less anticoagulation during tratment than CRRT
- It is an alternative option in resource-limiting settings

- **Disadvantages**
- Increased risk of hypotension

IHD are the most used RRT in the contest of non-ICU setting.

Schefold et al. Critical Care 2014, 18:R11
http://ccforum.com/content/18/1/R11

CRITICAL CARE

RESEARCH Open Access

The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial

Joerg C Schefold[1*], Stephan von Haehling[2], Rene Pschowski[1,3], Thorsten Onno Bender[1], Cathrin Berkmann[1], Sophie Briegel[1], Dietrich Hasper[1] and Achim Jörres[1]

RCT

Daily HD, 4 hours vs CVVH 35 ml/Kg/hour

switching of modality occurred in about 20% of intermittent hemodialysis (IHD) patients due to hemodynamic instability and/or significant fluid overload. In the continuous RRT group, switching of modality was indicated in 46% of cases because of repeated filter clotting, metabolic reasons, bleeding or issues with anticoagulation, thrombocytopenia or clinical improvement

Schefold *et al. Critical Care* 2014, **18**:R11

Renal replacement therapy in the ICU
VS non-ICU setting

SLED
(Sustained low efficiency dialysis)

- SLED is is a modified form of IHD, with low dialysate and blood flow rate, and more prolonged duration than IHD

- Advantages
- Better hemodynamic stability compare to IHD;
- It has faster fluid and solutes removal than CRRT but slower than IHD;
- It is an alternative option in resource-limiting settings

Seven RCTs and ten observational studies show no significant differences in recovery of renal function, fluid removal, days in ICU stay, and biochemical clearance between SLED and CRRT.

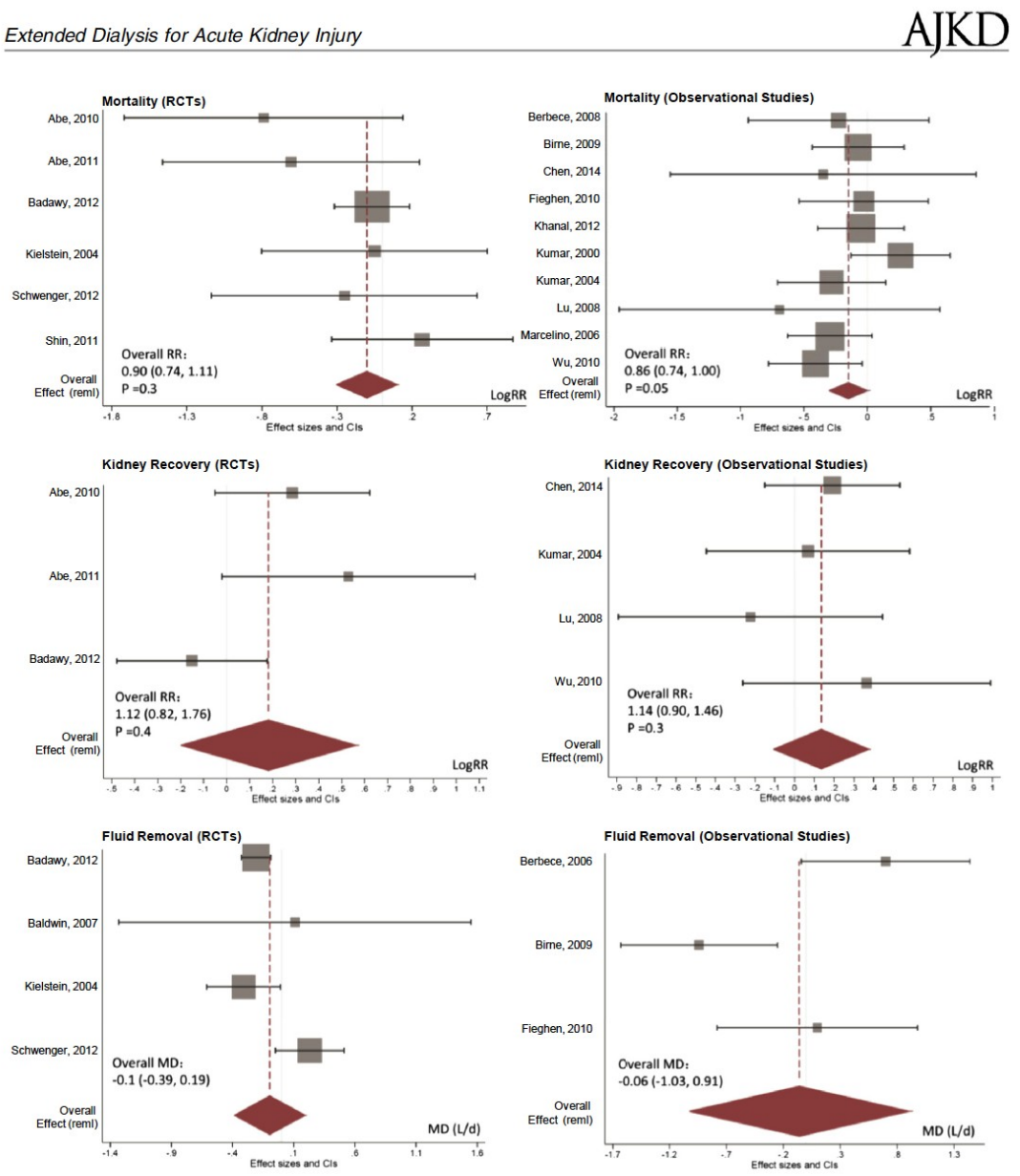
SLED is used in both context.

AJKD
Original Investigation

Extended Daily Dialysis Versus Continuous Renal Replacement Therapy for Acute Kidney Injury: A Meta-analysis

Ling Zhang, MD,[1,2] Jiqiao Yang, MD,[3] Glenn M. Eastwood, MD,[2] Guijun Zhu, MD,[2,4] Aiko Tanaka, MD,[2] and Rinaldo Bellomo, MD, PhD[2]

- 17 studies from 2000 to 2014 (7 RCTs and 10 observational studies)
- No difference in mortality rates between EDD and CRRT (relative risk, 0.90; 95% CI, 0.74-1.11; P 5 0.3).
- EDD was associated with lower mortality risk compared with CRRT in observational studies (relative risk, 0.86; 95% CI, 0.74-1.00; P 5 0.05)



Renal replacement therapy in the ICU
VS non-ICU setting

SCUF
(Slow continous ultrafiltration)

- SCUF is a simple ultrafiltration aimed to reduce the patient's overload and optimize fluid balance
- SCUF is indicated for patients with chronic or acute heart failure unresponsive to medical therapy

➢ **Avantages**

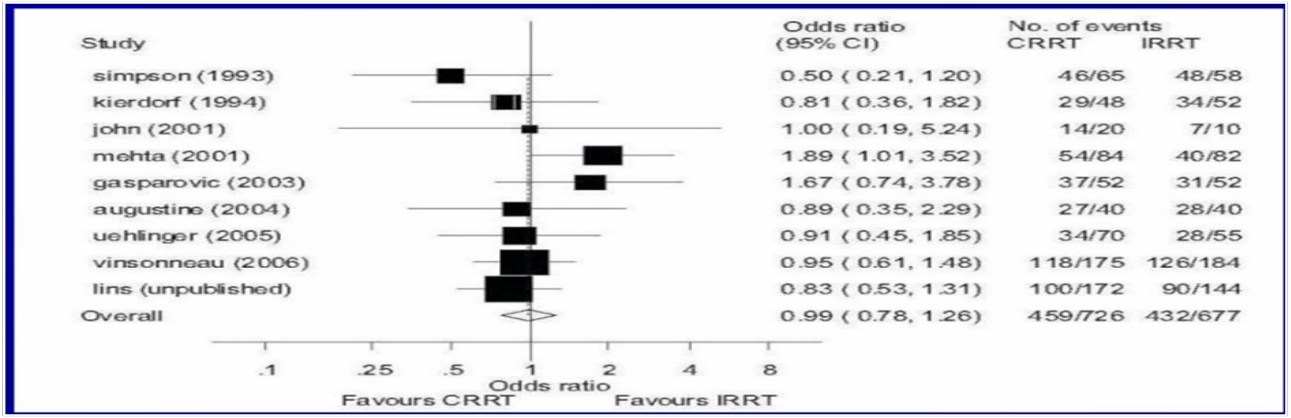
- Possibility to use a smaller-bore catheter in a peripheral vein as a vascular access.

SCUF is mainly used in cardiologic ICU.

Renal replacement therapy in AKI

No consensus on the optimal modality of RRT

Renal replacement therapy for acute kidney injury: let's follow the evidence.
Ronco C.



CRRT and HD are vastly different therapies that are not mutually exclusive but **rather are complementary** - they provide different options for patients at variable stages of their AKI course.

kidney INTERNATIONAL supplements

KDIGO Clinical Practice Guideline for Acute Kidney Injury

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)

Which RRT modality for AKI?

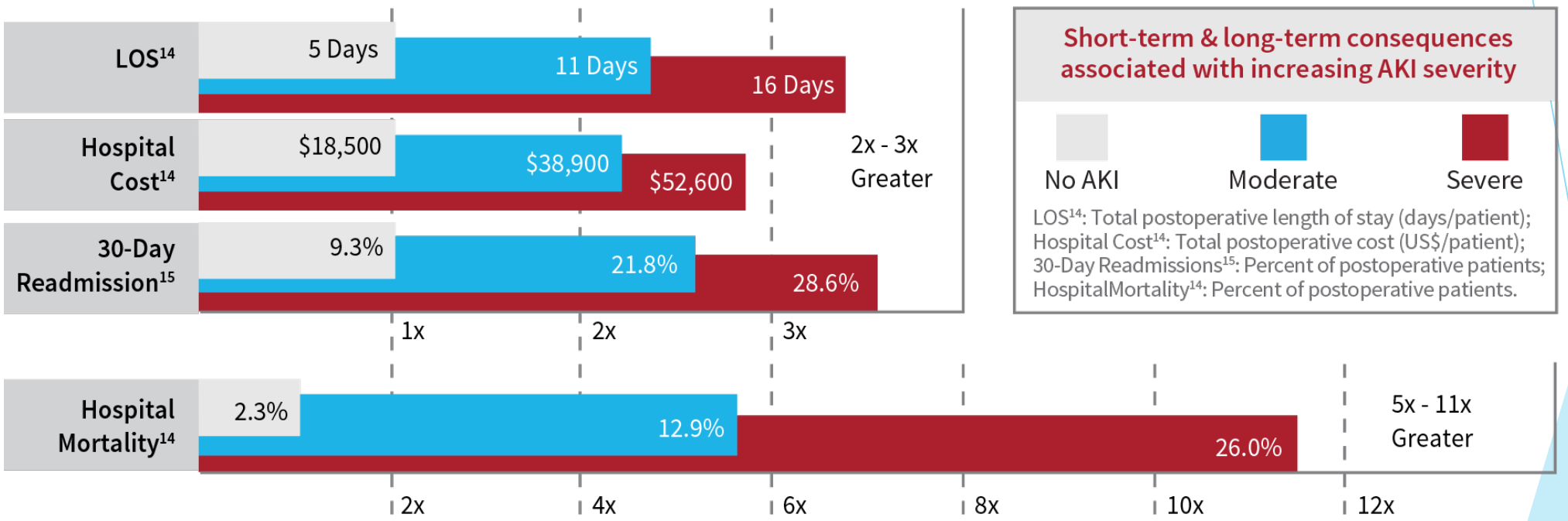
The old, good, clinical common sense

- Every RRT modality has advantages and adverse effects
- Different RRT modalities may be required in the clinical course of AKI in the same patient
- Switch from a modality-centered approach to a patient-centered approach
- Experience, logistis and costs are key players

Acute Kidney Injury treated with Dialysis: Differences between ICU and non-ICU setting

- Are they the same pathology?
- Are they treated at the same way?
- **Do they have the same outcomes?**

The Acute Kidney Injury effects



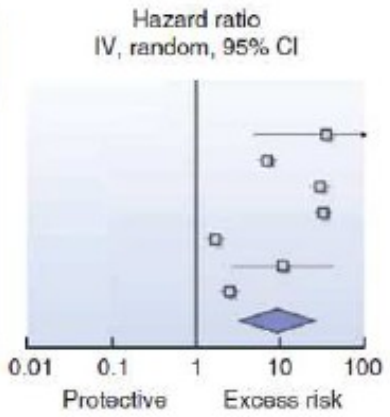
Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis

Steven G. Coca[1,2,3], Swathi Singanamala[1,3] and Chirag R. Parikh[1,2]

a

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Weiss *et al.* (13)	10.0	32.79 (4.30–249.77)
Amdur *et al.* (22)	15.5	6.64 (5.05–8.74)
Lo *et al.* (11)	15.5	28.08 (21.01–37.53)
James *et al.* (16)	15.6	29.99 (24.32–36.99)
James *et al.* (15,23)	15.5	1.60 (1.20–2.14)
Ando *et al.* (19)	12.4	9.91 (2.48–39.63)
Ishani *et al.* (21)	15.6	2.33 (1.83–2.96)
Total (95% CI)	100.0	8.82 (3.05–25.48)

Heterogeneity: $\tau^2 = 1.87$; $\chi^2 = 446.89$, d.f. = 6 ($P < 0.00001$); $I^2 = 99\%$. Test for overall effect: $Z = 4.02$ ($P < 0.0001$)

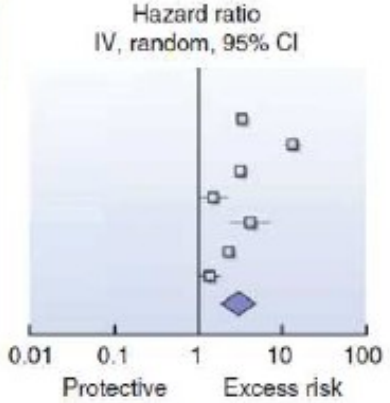


Il rischio di progredire verso una CKD e' aumentato di 10 volte

b

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Newsome *et al.* (14)	15.0	3.26 (2.87–3.70)
Ishani *et al.* (20)	14.8	12.99 (10.57–15.96)
Wald *et al.* (17)	14.9	3.22 (2.70–3.85)
Hsu *et al.* (10)	13.5	1.47 (0.95–2.28)
James *et al.* (15,23)	12.5	4.15 (2.32–7.41)
Lafrance *et al.* (18)	15.0	2.33 (2.08–2.61)
Choi *et al.* (12)	14.4	1.37 (1.02–1.84)
Total (95% CI)	100.0	3.10 (1.91–5.03)

Heterogeneity: $\tau^2 = 0.40$; $\chi^2 = 252.85$, d.f. = 6 ($P < 0.00001$); $I^2 = 98\%$. Test for overall effect: $Z = 4.58$ ($P < 0.00001$)



Il rischio di dialisi cronica e' aumentato di 4 volte

Kidney International (2012) **81,** 442–448;

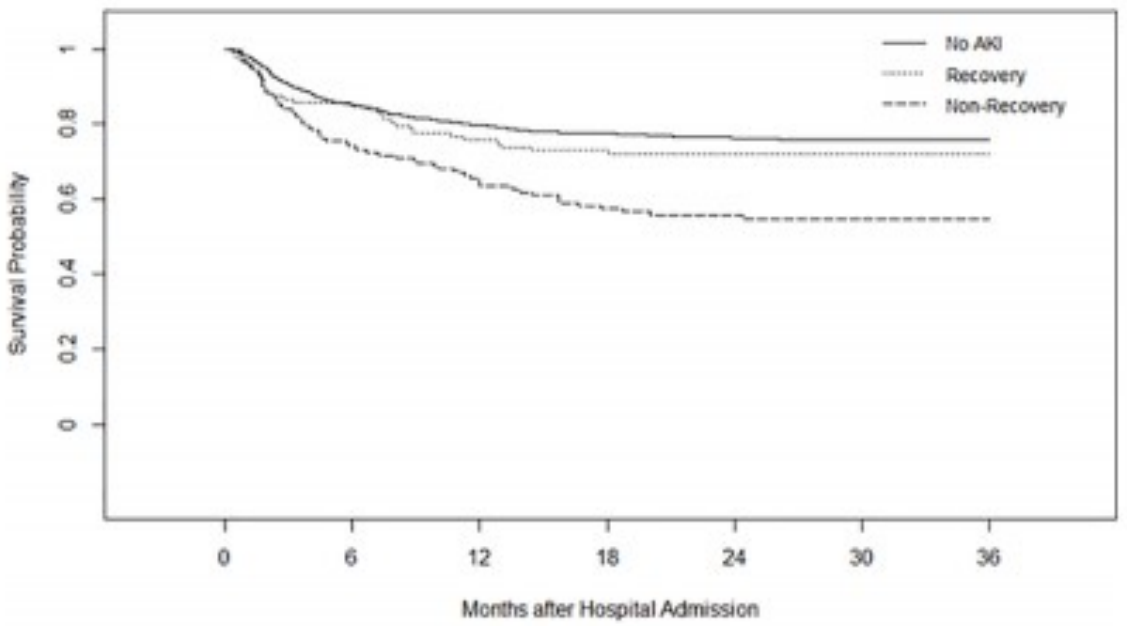
Long-term survival in patients with septic acute kidney injury is strongly influenced by renal recovery

Marco Fiorentino[1,2☯], Fadi A. Tohme[1,3,4☯], Shu Wang[1,5], Raghavan Murugan[1,3], Derek C. Angus[3], John A. Kellum[1,3,4*]

A multicenter study of pneumonia and sepsis

GenIMS

Genetic and Inflammatory Markers of Sepsis



Number of subjects at risk	0	6	12	18	24	30	36
No AKI	1480 (100%)	1261 (85%)	1180 (79.7%)	979 (66%)	496 (33.5%)	196 (13.2%)	25 (1.6%)
Recovery	111 (100%)	94 (84.6%)	84 (75.6%)	70 (63%)	37 (33.3%)	20 (18%)	6 (5.4%)
Non recovery	151 (100%)	112 (74.2%)	97 (64.2%)	77 (50.9%)	41 (27.1%)	14 (9.2%)	3 (1.9%)

Fig 2. Kaplan-Meier survival curves stratified by recovery status. The three groups are significantly different overall, $p < 0.001$ (Peto-Peto-Prentice test).

Fiorentino et al. PLOS One 2018

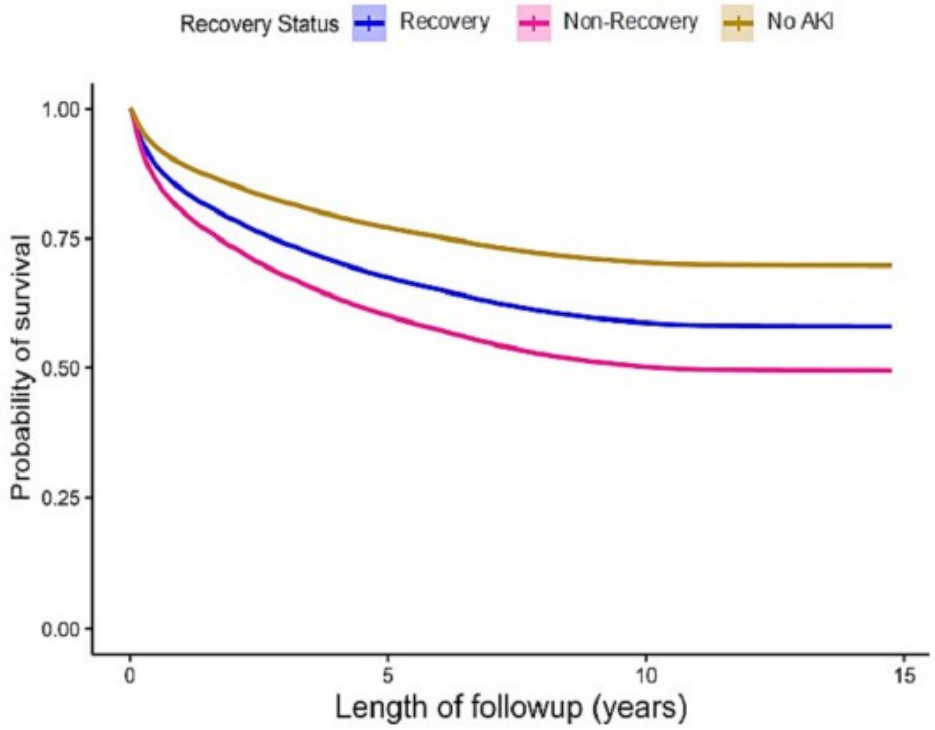
Contents lists available at ScienceDirect

Journal of Critical Care

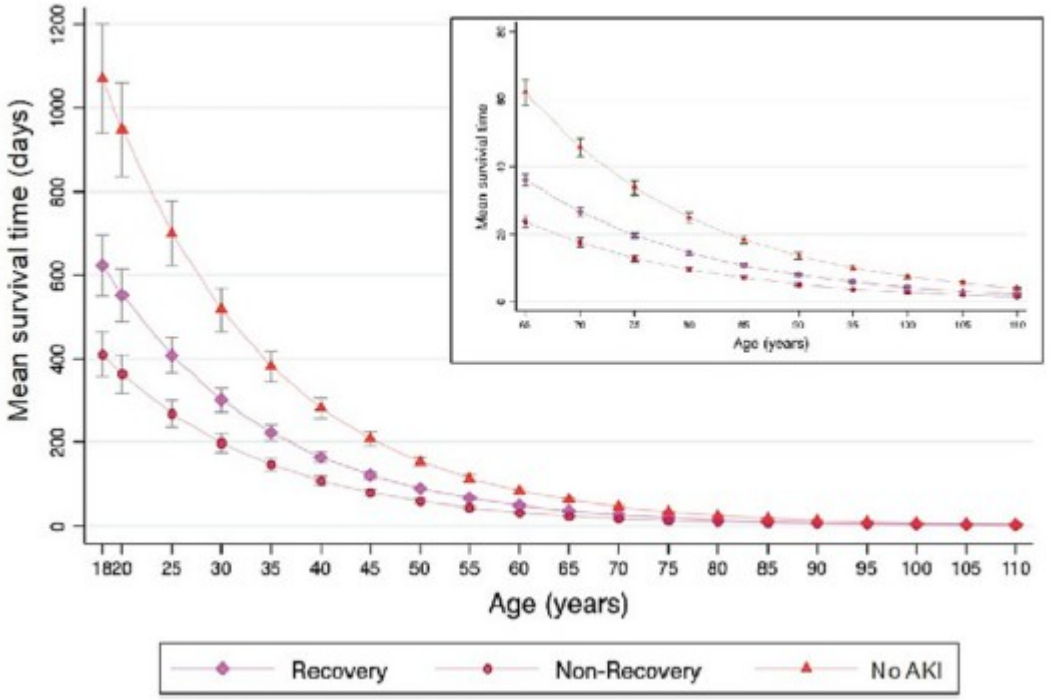
journal homepage: www.journals.elsevier.com/journal-of-critical-care

Recovery after AKI: Effects on outcomes over 15 years

Sadudee Peerapornratana [a,b,c,d,e], Marco Fiorentino [a,b,f], Priyanka Priyanka [a,b], Raghavan Murugan [a,b], John A. Kellum [a,b,*]



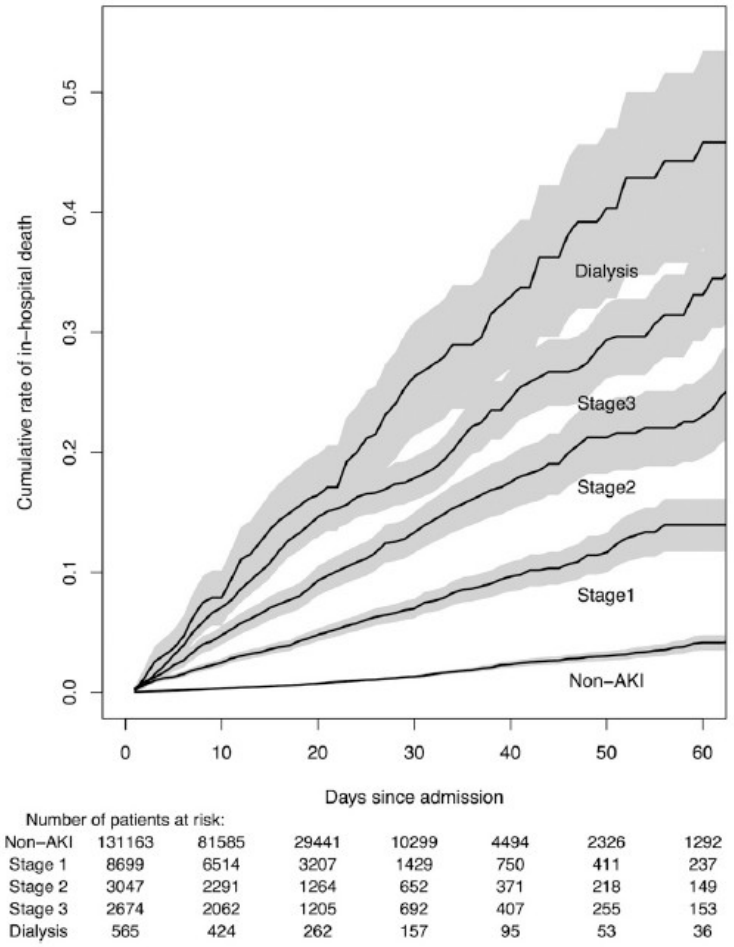
Adjusted Long term survival by AKI Recovery status. Adjusted by age,race,sex,multiple comorbidities



Age-adjusted Average Life expectancy by AKI recovery status at hospital discharge

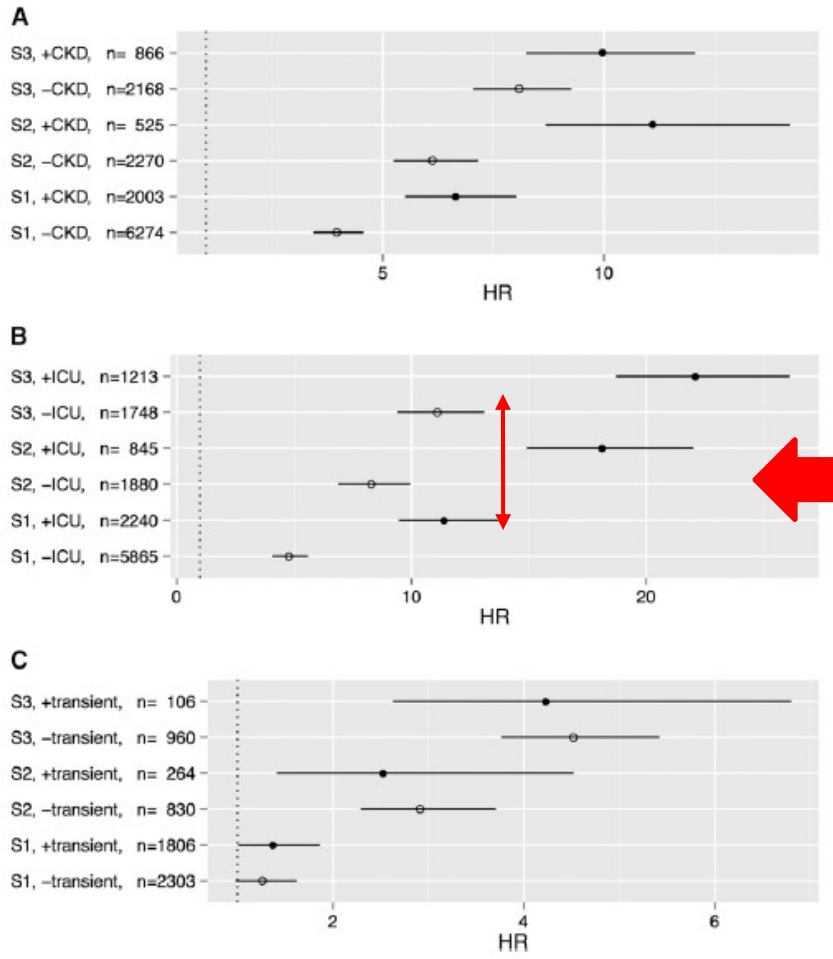
Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults

Xin Xu, Sheng Nie,* Zhangsuo Liu,† Chunbo Chen,‡ Gang Xu,§ Yan Zha,‖ Jing Qian,¶ Bicheng Liu,** Shuai Han,†† Anping Xu,‡‡ Xing Xu,* and Fan Fan Hou**



Number of patients at risk:

Non−AKI	131163	81585	29441	10299	4494	2326	1292
Stage 1	8699	6514	3207	1429	750	411	237
Stage 2	3047	2291	1264	652	371	218	149
Stage 3	2674	2062	1205	692	407	255	153
Dialysis	565	424	262	157	95	53	36



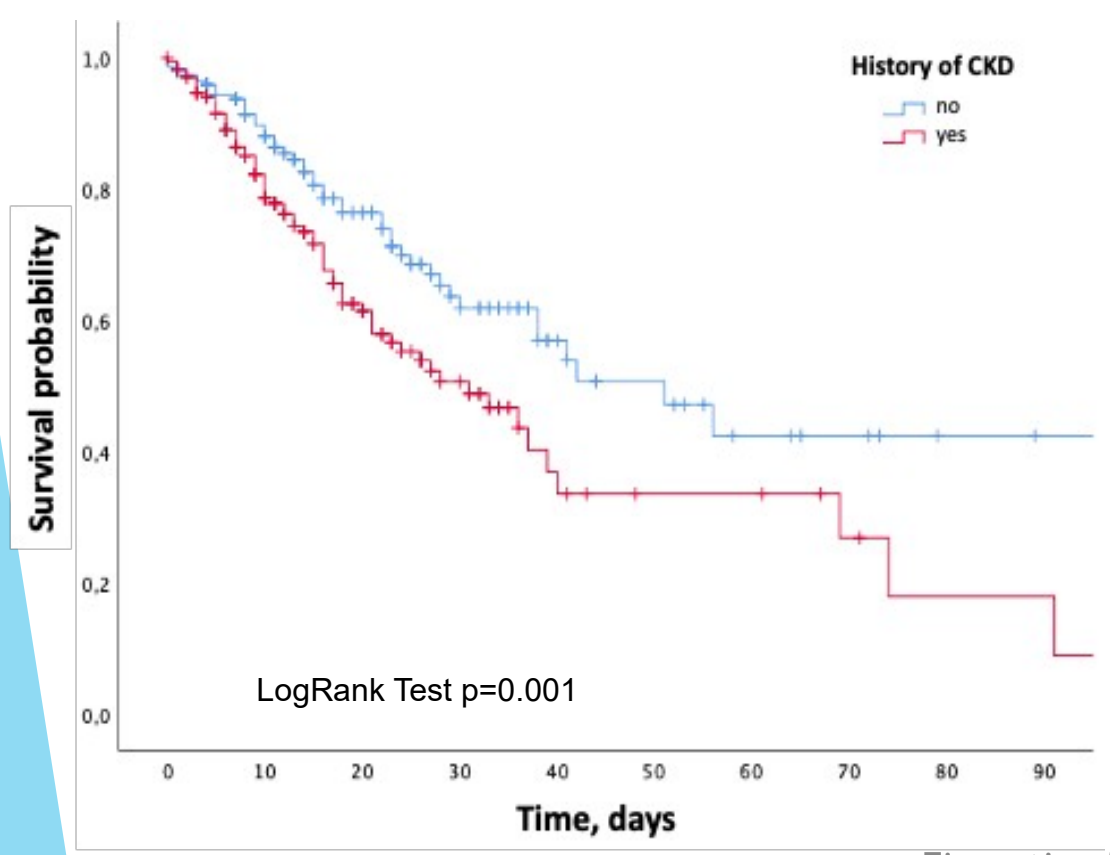
The mortality among patients with Hospital-Acquired-AKI (10.6%) was higher than that among patients with Community-Acquired-AKI (4.7%)

Clin J Am Soc Nephrol 10: 1510–1518, 2015.

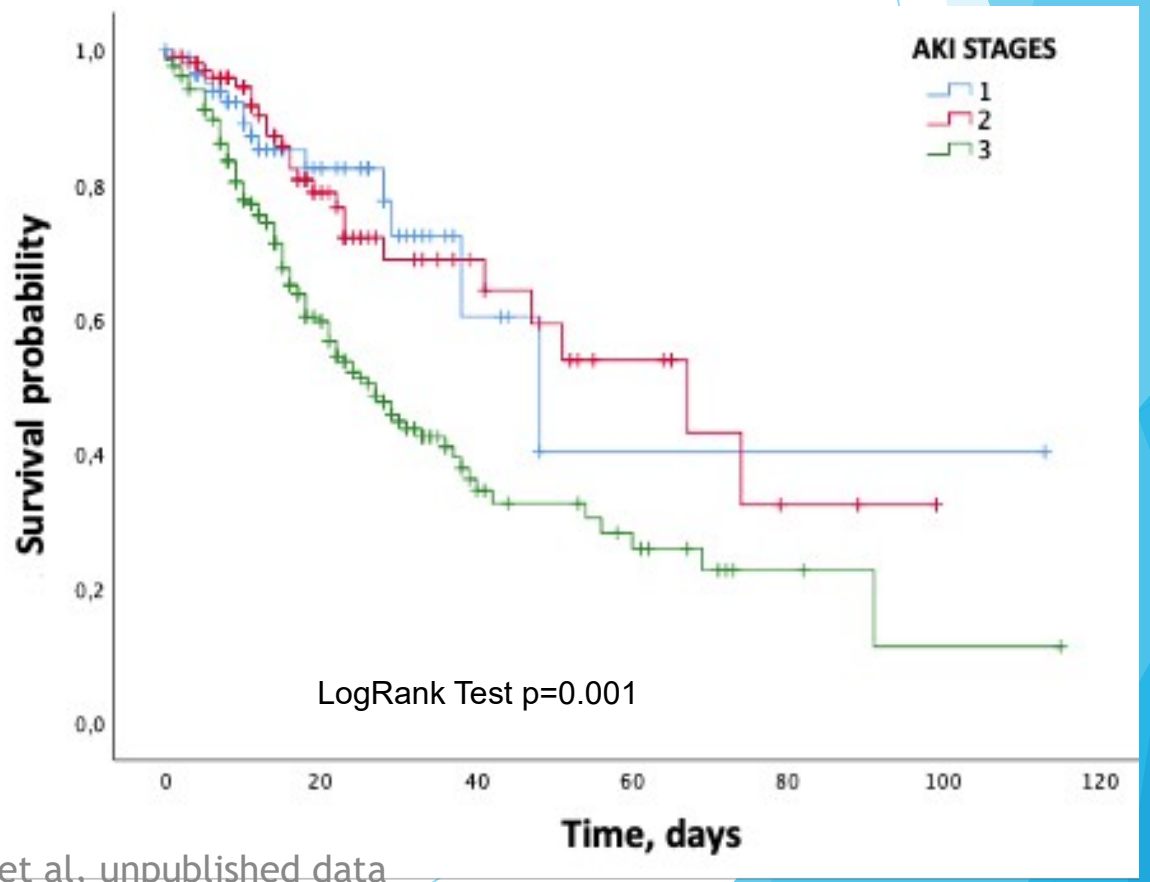
In-hospital survival

153 (36.9%) patients died during hospitalization

In-hospital survival probability stratified according to baseline eGFR



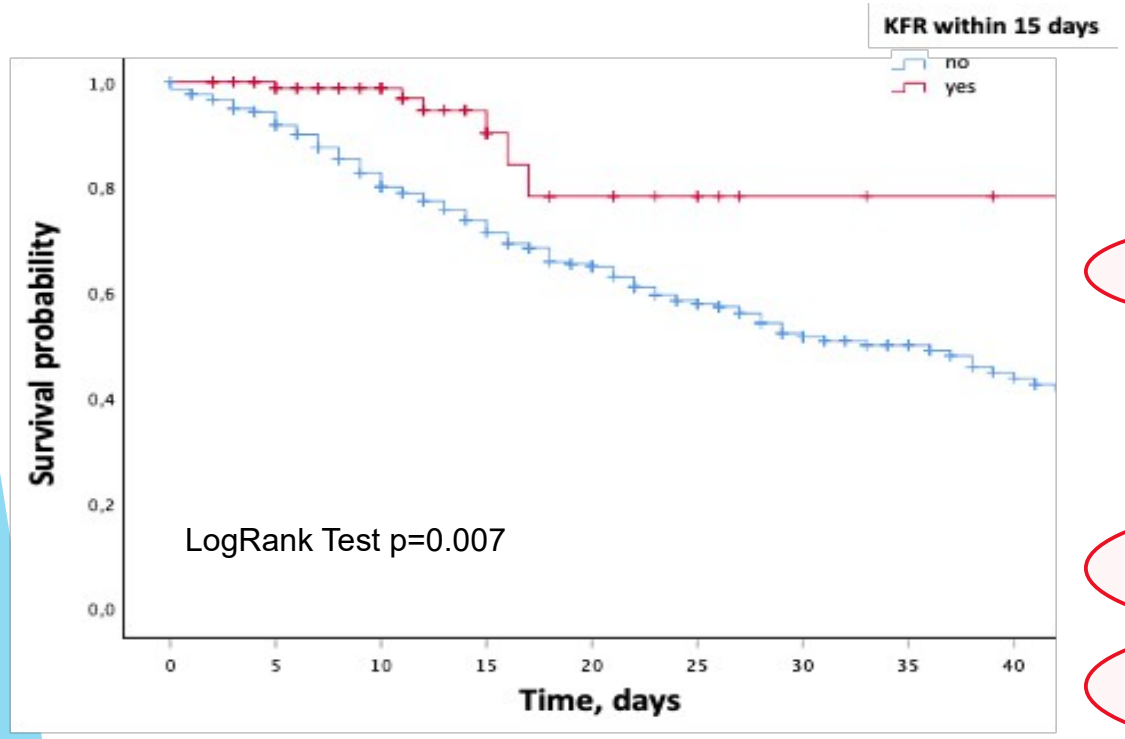
In-hospital survival probability stratified according to AKI stages



Fiorentino M et al, unpublished data

In-hospital survival

In-hospital survival probability stratified according to KFR

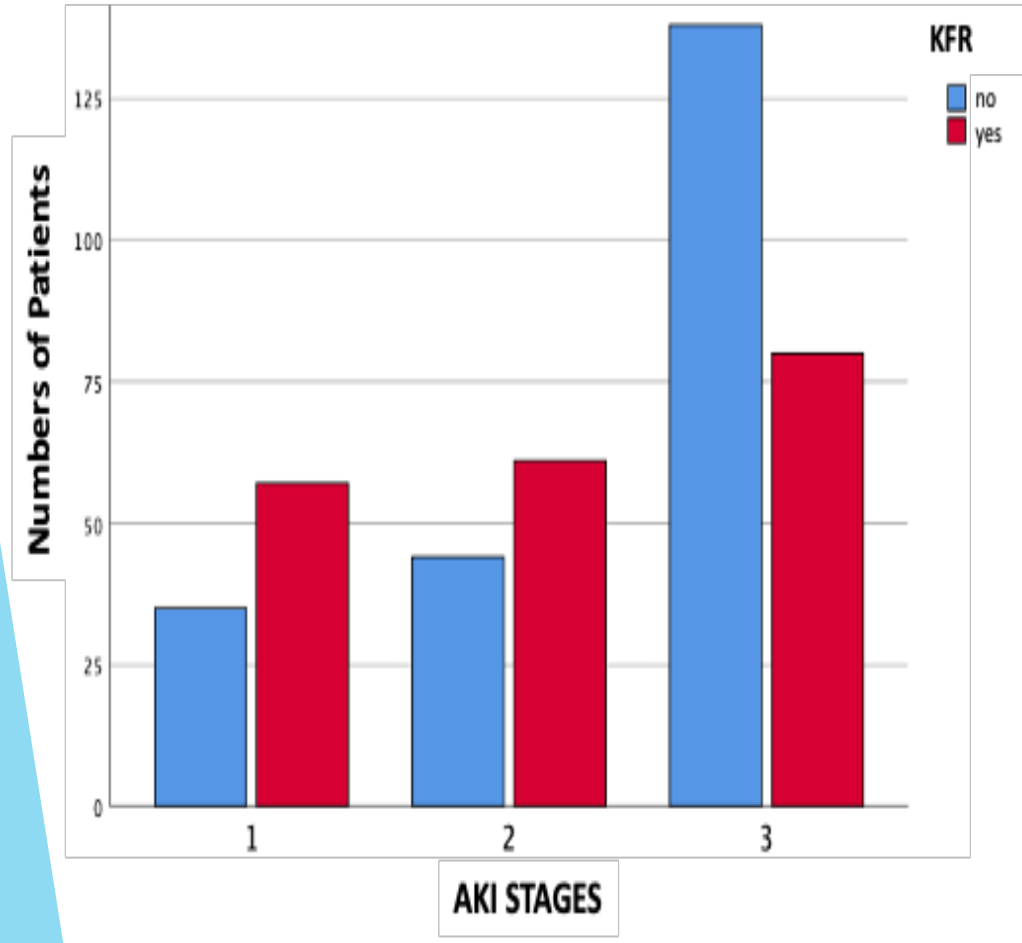


	Univariate Cox regression			Multivariate Cox regression		
	Crude HR	**95%CI**	**p-value**	**Adjusted HR**	**95%CI**	**p-value**
Age (years)	1.033	1.018-1.048	<0.001	1.032	1.012-1.053	**0.002**
Gender (M/F)	0.941	0.675-1.313	0.721	0.896	0.582-1.379	0.618
Baseline eGFR (ml/min/1,73m^2)	0.991	0.983-0.999	0.024	0.998	0.99-1.007	0.676
AKI classification (pre-renal vs renal AKI)	3.191	1.624-6.270	0.001	2.828	1.219-6.536	**0.015**
Kidney function recovery within 15 days	0.258	0.113-0.590	0.001	0.246	0.098-0.615	**0.003**

Fiorentino M et al, unpublished data

Kidney function recovery after AKI

KFR was observed in 197 out of 415 patients (47.5%)



Univariate and multivariate logistic regression analyses of risk factors with kidney function recovery

	Univariate Cox regression			Multivariate Cox regression		
	Crude OR	**95%CI**	**p-value**	**Adjusted OR**	**95%CI**	**p-value**
Age (years)	0.982	0.969-0.996	0.009	0.984	0.966-1.004	0.113
Gender (M/F)	0.927	0.627-1.372	0.705	0.636	0.384-1.051	0.077
Baseline eGFR (ml/min/1,73m^2)	1.026	1.016-1.036	<0.001	1.027	1.015-1.038	**<0.001**
AKI stages (stage 3 vs stages 1-2)	0.388	0.261-0.577	<0.001	0.401	0.235-0.683	**0.001**
RRT requiring AKI	0.209	0.102-0.428	<0.001	0.451	0.189-1.077	0.073
AKI setting (CA-AKI vs HA-AKI)	1.497	1.013-2.210	0.043	1.307	0.799-2.137	0.287

Fiorentino M et al, unpublished data

AKI-D outside ICU….outcomes

	AKI-D (n=54)	**AKI non D (n=361)**	P-value
Days on AKI	16 (10-31)	16 (9.7-31)	
Days on RRT	10 (3-19.5)		
Renal recovery after AKI	11 (20.3%)	184 (51.1%)	<0.001
Dialysis dependence at hospital discharge	11 (20.3%)		
Transfer to ICU	19 (35.1%)	11 (3.1%)	<0.001
Length of hospital stay, days, median (IQR)	15 (8 - 27)	15 (8-26)	
In-hospital death	28 (51.8%)	124 (34.3)	0.01

Fiorentino M et al, unpublished data

Conclusions

- Are they the same pathology?

Similar pathophysiological mechanisms and causes of AKI.
Different epidemiology

- Are they treated at the same way?

Personalized approach based on patients' needs

- Do they have the same outcomes?

Few data available. Worst outcomes compared to AKI non D